

## Predictors of Primary Atrial Fibrillation and Concomitant Clinical and Hemodynamic Changes in Patients With Chronic Heart Failure: A Prospective Study in 344 Patients With Baseline Sinus Rhythm

MASSIMO POZZOLI, MD, FESC, GIOVANNI CIOFFI, MD,\* EGIDIO TRAVERSI, MD,  
GIAN DOMENICO PINNA, MS, FRANCO COBELLI, MD, LUIGI TAVAZZI, MD, FESC, FACC†

Montescano, Pavia and Arco di Trento, Italy

**Objectives.** This study investigated the incidence, predisposing factors and significance of the onset of atrial fibrillation (AF) in patients with chronic congestive heart failure (CHF).

**Background.** The association between CHF and AF is well documented, but the factors that predispose to the onset of the arrhythmia and its impact remain controversial.

**Methods.** We prospectively followed up 344 patients with CHF and sinus rhythm (SR). Over a period of  $19 \pm 12$  months (mean  $\pm$  SD), 28 patients developed atrial fibrillation (AF), which became chronic in 18.

**Results.** At baseline, no differences were found in any clinical and hemodynamic variables between patients who developed chronic AF and those who did not. Reversible AF occurring during follow-up and lower mitral flow velocity at atrial contraction as detected at the last evaluation in SR were independent predictors of the subsequent development of chronic AF. When AF occurred, New York Heart Association functional class worsened (from

$2.4 \pm 0.5$  to  $2.9 \pm 0.6$ ,  $p = 0.0001$ ), peak exercise oxygen consumption declined (from  $16 \pm 5$  to  $11 \pm 5$  ml/kg per min,  $p = 0.002$ ), cardiac index decreased (from  $2.2 \pm 0.4$  to  $1.8 \pm 0.4$ ,  $p = 0.0008$ ), and mitral and tricuspid regurgitation increased (from grade  $1.8 \pm 1.1$  to grade  $2.4 \pm 1.4$ ,  $p = 0.0001$  and from grade  $1.0 \pm 1.2$  to grade  $1.8 \pm 1.2$ ,  $p = 0.001$ , respectively). Systemic thromboembolism occurred in 3 of the 18 patients with AF. Nine of 18 patients died after AF, and the occurrence of AF was a predictor of major cardiac events.

**Conclusions.** In patients with CHF, reversible AF and reduction of left atrial contribution to left ventricular filling predict the subsequent development of chronic AF. The onset of AF is associated with clinical and hemodynamic deterioration and may predispose to systemic thromboembolism and poorer prognosis.

(J Am Coll Cardiol 1998;32:197-204)

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Structural cardiac diseases underlie atrial fibrillation (AF) in 80% to 97% of patients, and chronic congestive heart failure (CHF) is one of its most frequent precursors (1,2). Whereas the association between CHF and AF is well documented, the factors that predispose to the onset of this arrhythmia are not. In addition, the clinical and hemodynamic impact of AF in patients with CHF remains controversial. Some studies (3-6) have shown that such patients have more compromised hemodynamic function, lower exercise capacity and a higher risk of developing systemic thromboembolic events and of dying than those with sinus rhythm (SR). However, these findings have not been confirmed by other studies (7-11). The heterogeneous patient groups investigated and the retrospective design

of some of these studies may account for the discrepancies. Accordingly, a large group of patients with CHF and SR was prospectively investigated to assess the incidence and the predictors of AF. We also investigated whether this arrhythmia, once developed, had any adverse consequences.

### Methods

**Study patients.** The study included 354 patients with CHF and SR consecutively admitted to our heart failure unit between September 1992 and May 1995 for evaluation for heart transplantation. All patients had experienced more than two episodes of CHF requiring hospital admission in the 6 months preceding the admission to our center. After admission, therapy was optimized to achieve a stable clinical condition. Ten patients with refractory CHF requiring infusion of inotropic or vasodilator medications, or both, were excluded from the analysis, leaving a final study group of 344 patients whose general characteristics are summarized in Table 1. All patients received diuretic drugs with a flexible regimen and high dose angiotensin-converting inhibitors, if tolerated. Digitalis was always administered if not contraindicated, and

From the Salvatore Maugeri Foundation, Institute of Care and Research, Montescano Medical Center, Montescano, Pavia; \*Rehabilitation Center Ermo, Arco di Trento, Trento; and †Division of Cardiology, Policlinico San Matteo, Institute of Care and Research, Pavia, Italy. This study was supported by the Salvatore Maugeri Foundation and was presented in part at the 69th Annual Scientific Sessions of the American Heart Association, New Orleans, Louisiana, November 1996.

Manuscript received August 25, 1997; revised manuscript received March 23, 1998, accepted April 9, 1998.

Address for correspondence: Dr. Massimo Pozzoli, Department of Cardiology, Montescano Medical Center, Montescano 27047, Pavia, Italy.

**Abbreviations and Acronyms**

AF	= atrial fibrillation
CHF	= chronic congestive heart failure
ECG	= electrocardiogram
INR	= international normalized ratio
OR	= odds ratio
SR	= sinus rhythm

amiodarone was usually given in the case of previous sustained atrial or ventricular arrhythmias.

**Measurements.** All investigations were performed after the patient's condition had been stabilized and therapy optimized according to clinical criteria. Venous blood was collected for routine measurements, including serum electrolytes and thyroid hormones and, in a subgroup of 206 consecutive patients, plasma norepinephrine was determined by high performance liquid chromatography. The amplitude and the duration of the P wave were recorded from a standard 12 lead surface electrocardiogram (ECG). Baroreflex sensitivity was assessed by the phenylephrine test using a previously described method (12).

Exercise capacity was assessed by a symptom-limited treadmill cardiopulmonary exercise test, and expiratory gases were analyzed using a Medical Graph System 2001 analyzer. Peak oxygen consumption was measured by averaging the value of the final 30 s of exercise.

Right heart catheterization was performed using a 7F Swan Ganz balloon-tipped catheter inserted into the right internal jugular vein and advanced through the right heart cavities into the pulmonary artery. Standard hemodynamic measurements were obtained using a 7005 Marquette polygraph. Cardiac output was measured by the thermodilution method.

Hewlett-Packard Sonos 1000 and 2500 systems with 2.5- and 3.5-MHz probes were used to perform Doppler and two-dimensional echocardiographic examinations. Left atrial and left ventricular diameters were measured by M-mode echocardiography according to the recommendations of the American Society of Echocardiography (13). Right and left atrial and left ventricular volumes were assessed by two-

dimensional apical two- and four-chamber views using the modified Simpson's rule. Atrial emptying fractions were calculated according to the formula: Maximal volume – Minimal volume/Maximal volume \* 100. Mitral and tricuspid regurgitations were diagnosed by color Doppler and quantified using a 4+ grading system (14). Mitral diastolic flow velocity was assessed by pulsed Doppler from the apical four-chamber view by positioning the sample volume between the leaflets at the level of their tips in diastole. The following measurements were averaged from five consecutive cycles: maximal early diastolic velocity, maximal late diastolic velocity, their ratio and the deceleration time of early diastolic velocity. When patients were in AF the measurements obtained in 10 cycles were analyzed.

**Follow-up.** Patients underwent serial clinical, laboratory, ergometric, hemodynamic and echocardiographic evaluations every 6 months. Between these intervals, telephone contact with the patients, next of kin, referral physicians and peripheral hospitals were used at intervals of 3 months to verify patient status. No patient was lost to follow-up.

The development of chronic AF was the primary end point in this study. When AF occurred, patients were admitted to the hospital, potential precipitating factors were searched for and treated; medical therapy was optimized to stabilize hemodynamic conditions and to control ventricular heart rate. Oral anticoagulant agents were given to all patients with AF, and the dose was adjusted to keep the international normalized ratio (INR) between 2 and 3. A low dose regimen of amiodarone was also started. About 4 weeks after anticoagulation, if the arrhythmia did not subside, transthoracic synchronized direct current cardioversion was attempted when not contraindicated (15). Left atrial dilation was not considered as an absolute contraindication. Patients in whom SR could not be restored, and AF was present at hospital discharge, and those in whom the arrhythmia recurred after an initially successful cardioversion, and its persistence was documented by serial ECGs, were considered as having *chronic AF* (Fig. 1). Paroxysmal AF, defined according to the criteria proposed by Levy et al. (16), and AF lasting >7 days and then successfully cardioverted were defined as *reversible AF* and analyzed together.

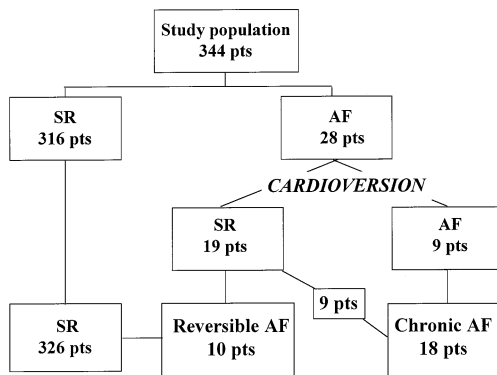
Once chronic AF developed, all patients were given digitalis, and six patients also received low dose amiodarone in an attempt to obtain adequate ventricular rate control. Then, to assess whether AF was associated with any clinical or hemodynamic deterioration, all patients underwent a complete reevaluation 3 ± 3 months after the onset of the arrhythmia.

The prognosis of patients who remained in SR and those who developed chronic AF was assessed by considering as major events *cardiac death* and *urgent heart transplantation*. Systemic thromboembolisms were separately considered minor events and classified as 1) *ischemic strokes*, defined as the abrupt onset of focal neurologic deficit in the distribution territory of a single brain artery persisting for >24 h and confirmed by a computed tomographic or magnetic resonance imaging scan; 2) *transient ischemic attacks*, defined as focal

**Table 1.** Principal Characteristics of 344 Study Patients at Entry

Age (yr)	54 ± 8
Men/women	303/41
NYHA functional class III/IV	166 (48%)
Peak VO <sub>2</sub> (ml/kg per min)	14 ± 5
Etiology of heart failure	
Idiopathic	166 (48%)
Ischemic	146 (43%)
Valvular	17 (5%)
Other	15 (4%)
Pulmonary artery wedge pressure (mm Hg)	20 ± 10
Cardiac index (liters/min per m <sup>2</sup> )	2.2 ± 0.4
Left ventricular ejection fraction (%)	23 ± 7

Data presented are mean value ± SD or number (%) of patients.



**Figure 1.** Flowchart showing the occurrence of AF in 344 patients (pts) with SR during follow-up. Twenty-eight patients (8%) developed AF. AF persisted in 9 patients despite cardioversion, whereas SR was restored in 19 patients. SR persisted in 10 of these 19 patients throughout the follow-up, whereas AF occurred in the remaining 9, and SR could not be restored. Thus, overall, 18 patients (5%) developed chronic AF.

deficits lasting <24 h; 3) *peripheral embolization*, defined as an abrupt vascular insufficiency in any peripheral area associated with evidence of arterial occlusion in the absence of other likely mechanisms.

**Statistical analysis.** Results are given as mean value  $\pm$  SD. The unpaired Student test and a Fisher exact test were used to compare differences of continuous and categorical variables, respectively, in patients with and without AF. Variables for which a significant difference was observed between the two groups were used as candidate predictors of AF in a multivariate logistic regression model. Model identification was performed according to a stepwise procedure using a p value of 0.05 as the threshold for entrance to or removal from the model.

To be confident that the observed changes of clinical and instrumental variables over time were not affected by different baseline conditions, a statistically matched control group of patients with stable SR was selected, as follows: a Gower's generalized distance from each of the patients who developed AF during follow-up and all the patients who remained in SR was computed and ranked in ascending order. The distance was calculated using the following variables: age, New York Heart Association functional class, exercise capacity, pulmonary artery wedge pressure, cardiac index and mitral and tricuspid regurgitations. The control group was then defined by taking, for each patient who developed AF, the two closest patients with SR who had had at least two serial evaluations. Analysis of variance was then used to compare changes in the variables tested between the two groups and was assessed by testing for the interaction between the factor time and the factor group.

To verify whether the development of AF had an adverse prognostic effect (cardiac death and urgent heart transplantation), logistic regression analysis was performed. Because the time to the onset of AF may vary widely among subjects, exerting a confounding effect on the prognostic value of AF,

we attempted to minimize the effect of time by categorizing the follow-up time into five periods lasting 300 days.

All statistical analyses were carried out using the SAS/STAT statistical package, revision 6.10 (17). A p value < 0.05 was considered statistically significant.

## Results

**Development of AF.** During a follow-up period of  $19 \pm 12$  months, AF developed in 28 patients. AF persisted despite cardioversion in 9 patients, whereas SR was restored by pharmacologic (9) or electrical cardioversion (10) in 19. In 10 of these 19 patients, SR persisted throughout follow-up, whereas AF reoccurred in 9, and SR could not be restored. Thus, 18 patients (5%) overall developed chronic AF (Fig. 1).

At baseline, patients who developed chronic AF did not differ from those who remained in SR for any variable tested. This result was valid both for all patients enrolled in the study and for the subgroup of patients who survived free of heart transplantation at least 6 months (who therefore had had at least two evaluations in SR) (Table 2, left-hand columns). When the variables measured in the two groups at the last evaluation (for patients who developed AF we considered the last evaluation in SR, obtained  $3 \pm 3$  months before the onset of the arrhythmia) were considered, maximal late diastolic velocity of mitral flow was significantly lower in patients who subsequently experienced AF than in patients with stable SR, whereas maximal early diastolic velocity was higher in the former than in the latter. Left atrial emptying fraction was also more compromised in patients with subsequent AF. No differences were found in hemodynamic variables, and within the clinical variables, only previous reversible AF was significantly ( $p = 0.0001$ ) associated with late development of chronic AF (Table 2, right-hand columns). Regression logistic analysis retained previously reversible AF (Wald chi-square 17.8, odds ratio [OR] 55.2,  $p = 0.0001$ ) and reduced maximal late diastolic mitral flow velocity (Wald chi-square 6.9, OR 1.3,  $p = 0.005$ ), measured during the last evaluation in SR, as independent predictors of the onset of chronic AF. The sensitivity of the model, using a threshold probability value of 0.5, for predicting the onset of the arrhythmia was 99%, whereas the specificity was only 19%.

When the 18 patients who developed chronic AF were compared with the 10 patients in whom the AF reverted to SR, the only significant difference found was in late diastolic mitral flow velocity ( $25 \pm 14$  vs.  $48 \pm 24$  cm/s,  $p = 0.03$ ), whereas hemodynamic variables, atrial volumes and severity of atrio-ventricular valve regurgitation did not predict the success of the cardioversion.

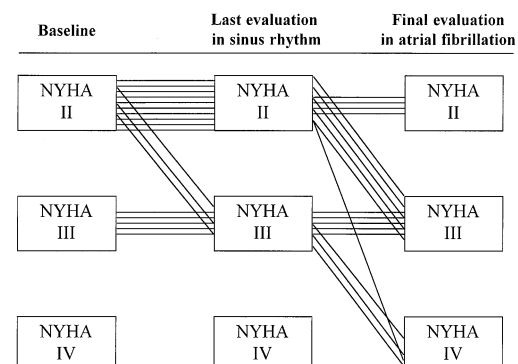
**Clinical and hemodynamic changes associated with onset of AF.** In eight patients the onset of AF was accompanied by overt heart decompensation. In most cases the arrhythmia occurred when patients were at home, so it was not possible to establish with certainty whether its onset preceded or followed heart decompensation. In the remaining 10 patients clinical status was relatively stable. In all but four patients, who

**Table 2.** Characteristics of Patients With Sinus Rhythm Classified According to Development of Chronic Atrial Fibrillation During Follow-Up\*

Variable	Baseline Evaluation			Last Evaluation in SR		
	Subsequent Chronic AF (n = 18)	Stable SR (n = 290)	p Value	Subsequent Chronic AF (n = 18)	Stable SR (n = 290)	p Value
<b>Clinical</b>						
Age (yr)	54 ± 10	54 ± 8	NS			
Men/women	14/4	255/35	NS			
NYHA functional class	2.3 ± 0.5	2.3 ± 0.5	NS	2.4 ± 0.5	2.6 ± 0.6	NS
Serum sodium (mEq/liter)	137 ± 4	138 ± 3	NS	137 ± 3	138 ± 10	NS
Heart rate (beats/min)	72 ± 16	76 ± 14	NS	75 ± 13	73 ± 13	NS
Valvular etiology of heart failure	3 (12%)	13 (4%)	NS			
<b>Ergometry</b>						
Maximal heart rate (beats/min)	131 ± 18	126 ± 21	NS	130 ± 19	124 ± 20	NS
Peak $\text{VO}_2$ (ml/kg per min)	16 ± 4	14 ± 5	NS	16 ± 5	15 ± 5	NS
<b>Neurohormonal pattern</b>						
Norepinephrine (pg/ml)	332 ± 194	355 ± 210	NS	340 ± 154	379 ± 224	NS
Thyrotropin (mU/liter)	1.6 ± 0.9	2.3 ± 2	NS	1.7 ± 0.9	2.2 ± 1.8	NS
Free thyroxine (ng/100 ml)	1.8 ± 0.5	1.5 ± 0.6	NS	1.9 ± 0.5	1.5 ± 0.6	NS
Free three iodothyronine (pg/ml)	7.3 ± 4	7.3 ± 5	NS	8.1 ± 4	7.2 ± 4	NS
<b>Electrocardiography</b>						
Maximal P wave amplitude (mV)	0.16 ± 0.06	0.19 ± 0.08	NS	0.17 ± 0.09	0.18 ± 0.07	NS
Maximal P wave duration (ms)	96 ± 40	138 ± 55	NS	108 ± 60	132 ± 71	NS
Episodes of reversible AF during follow-up				9 (50%)	10 (3%)	0.0001
Baroreflex sensitivity (ms/mm Hg)	3.2 ± 2	4.5 ± 4	NS	3.0 ± 2	5.0 ± 4	NS
<b>Hemodynamic pattern</b>						
Pulmonary artery wedge pressure (mm Hg)	23 ± 9	19 ± 10	NS	21 ± 7	18 ± 10	NS
Right atrial pressure (mm Hg)	7 ± 5	5 ± 4	NS	7 ± 6	5.2 ± 4	NS
Cardiac index (liter/min per $\text{m}^2$ )	2.1 ± 0.4	2.2 ± 0.5	NS	2.2 ± 0.4	2.2 ± 0.6	NS
<b>Echocardiography</b>						
Left ventricular ejection fraction (%)	24 ± 6	23 ± 7	NS	25 ± 7	24 ± 7	NS
Left ventricular end-diastolic diameter (mm)	73 ± 14	72 ± 10	NS	74 ± 14	72 ± 10	NS
Maximal left atrial volume (ml)	78 ± 22	82 ± 50	NS	90 ± 25	81 ± 63	NS
Maximal right atrial volume (ml)	59 ± 38	57 ± 35	NS	66 ± 37	55 ± 34	NS
Left atrial emptying fraction (%)	26 ± 10	31 ± 16	NS	19 ± 18	32 ± 14	0.005
Right atrial emptying fraction (%)	23 ± 14	32 ± 14	NS	28 ± 12	32 ± 14	NS
Tricuspid regurgitation (4-grade score)	0.7 ± 1	1 ± 1	NS	1 ± 1.2	1 ± 1.1	NS
Mitral regurgitation (4-grade score)	1.4 ± 1	1.8 ± 1.2	NS	1.8 ± 1.1	1.9 ± 1.2	NS
Maximal early diastolic mitral flow velocity (cm/s)	73 ± 26	74 ± 26	NS	95 ± 19	73 ± 26	0.02
Maximal late diastolic mitral flow velocity (cm/s)	37 ± 12	42 ± 23	NS	25 ± 14	45 ± 25	0.04
Early diastolic deceleration time of transmitral flow (ms)	118 ± 32	132 ± 54	NS	121 ± 32	151 ± 64	NS

\*Only patients with at least two evaluations in SR were considered. Data presented are mean value ± SD or number (%) of patients. AF = atrial fibrillation; SR = sinus rhythm; other abbreviations as in Table 1.

remained in functional class IV, clinical conditions could be stabilized by adjusting medical therapy, and in no patient did the hemodynamic deterioration prompt urgent cardioversion. However, even after therapy optimization, the functional class deteriorated in 9 of 18 patients (Fig. 2). Concomitantly, peak oxygen consumption, which had been stable during follow-up when the patients were in SR, had decreased in the first evaluation after development of AF from  $16 \pm 5$  to  $11 \pm 5$  ml/kg per min despite an increase in heart rate at peak exercise (Table 3). Again in the first evaluation after the onset of AF, cardiac index markedly decreased (Fig. 3), the severity of tricuspid and mitral regurgitation increased, and both right and left atrial volumes increased further (Fig. 4, Table 3). Left ventricular dimensions and ejection fractions remained unchanged. The matched patients who remained in stable SR did

**Figure 2.** Changes in New York Heart Association (NYHA) functional class in the 18 patients who developed chronic AF before and after the onset of AF.



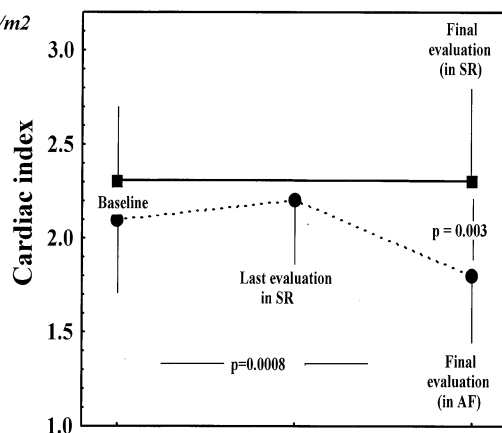
**Table 3.** Changes in Clinical, Hemodynamic and Echocardiographic Variables Observed in 18 Patients Who Developed Chronic Atrial Fibrillation During Follow-Up and in 36 Matched Patients With Sinus Rhythm

Variable	AF Group (mean $\pm$ SD) (n = 18)				Control Group (mean $\pm$ SD) (n = 36)		
	Baseline	Last Evaluation in SR	Final Evaluation in AF	p Value	Baseline	Last Evaluation	p Value
<b>Clinical</b>							
NYHA functional class	2.3 $\pm$ 0.5	2.4 $\pm$ 0.5	2.9 $\pm$ 0.6*	0.0001	2.2 $\pm$ 0.4	2.6 $\pm$ 0.5	0.0001
Heart rate (beats/min)	72 $\pm$ 16	75 $\pm$ 13	78 $\pm$ 10	NS	84 $\pm$ 15	82 $\pm$ 14	NS
Maximal heart rate exercise (beats/min)	131 $\pm$ 18	130 $\pm$ 19	140 $\pm$ 24*	0.03	127 $\pm$ 9	124 $\pm$ 6	NS
Peak VO <sub>2</sub> (ml/kg per min)	16 $\pm$ 4	16 $\pm$ 5	11 $\pm$ 5*	0.002	14 $\pm$ 4	14 $\pm$ 5	NS
<b>Hemodynamic pattern</b>							
Systolic blood pressure (mm Hg)	107 $\pm$ 6	106 $\pm$ 7	104 $\pm$ 6	NS	108 $\pm$ 7	107 $\pm$ 6	NS
Pulmonary artery wedge pressure (mm Hg)	23 $\pm$ 9	21 $\pm$ 7	24 $\pm$ 7	NS	19 $\pm$ 8	18 $\pm$ 7	NS
Right atrial pressure (mm Hg)	7 $\pm$ 5	7 $\pm$ 6	9 $\pm$ 6	NS	5 $\pm$ 3	5 $\pm$ 4	NS
Cardiac index (liter/min per m <sup>2</sup> )	2.1 $\pm$ 0.4	2.2 $\pm$ 0.4	1.8 $\pm$ 0.4*	0.0008	2.4 $\pm$ 0.4	2.2 $\pm$ 0.5	NS
<b>Echocardiography</b>							
Left ventricular ejection fraction (%)	24 $\pm$ 6	25 $\pm$ 7	25 $\pm$ 6	NS	22 $\pm$ 5	23 $\pm$ 7	NS
Left ventricular end-diastolic diameter (mm)	73 $\pm$ 14	72 $\pm$ 10	74 $\pm$ 15	NS	74 $\pm$ 12	73 $\pm$ 11	NS
Maximal left atrial volume (ml)	78 $\pm$ 22	90 $\pm$ 25†	114 $\pm$ 33*	0.0001	61 $\pm$ 26	69 $\pm$ 27	NS
Maximal right atrial volume (ml)	59 $\pm$ 38	66 $\pm$ 37	82 $\pm$ 34*	0.0001	46 $\pm$ 21	50 $\pm$ 23	NS
Left atrial emptying fraction (%)	26 $\pm$ 10	19 $\pm$ 18		NS	36 $\pm$ 18	34 $\pm$ 15	NS
Right atrial emptying fraction (%)	23 $\pm$ 14	28 $\pm$ 12		NS	33 $\pm$ 14	36 $\pm$ 13	NS
Tricuspid regurgitation (4-grade score)	0.7 $\pm$ 1	1 $\pm$ 1.2	1.8 $\pm$ 1.2*	0.001	0.7 $\pm$ 1	0.9 $\pm$ 1	0.02
Mitral regurgitation (4-grade score)	1.4 $\pm$ 1	1.8 $\pm$ 1.1	2.4 $\pm$ 1.4*	0.0001	1.4 $\pm$ 1	1.6 $\pm$ 1	0.03
Maximal early diastolic mitral flow velocity (cm/s)	73 $\pm$ 26	95 $\pm$ 19†		0.006	72 $\pm$ 21	73 $\pm$ 23	NS
Maximal late diastolic mitral flow velocity (cm/s)	37 $\pm$ 12	25 $\pm$ 14†		0.0001	42 $\pm$ 22	48 $\pm$ 23	NS
Early diastolic deceleration time of transmitral flow (ms)	118 $\pm$ 32	121 $\pm$ 33		NS	126 $\pm$ 44	137 $\pm$ 59	NS

Statistically significant by pairwise comparison: \*last evaluation in sinus rhythm versus final evaluation in atrial fibrillation; †baseline versus last evaluation in sinus rhythm. Abbreviations as in Tables 1 and 2.

not show significant changes in most of the variables tested, and only functional class and mitral and tricuspid regurgitation significantly worsened (Table 3). Table 4 shows the significance of differences in variations during follow-up of measurements obtained in patients who developed AF (before and after the event) and in those who remained in SR.

**Figure 3.** Changes in cardiac index over time in patients who later developed chronic AF (circles) versus those who remained in SR (squares).

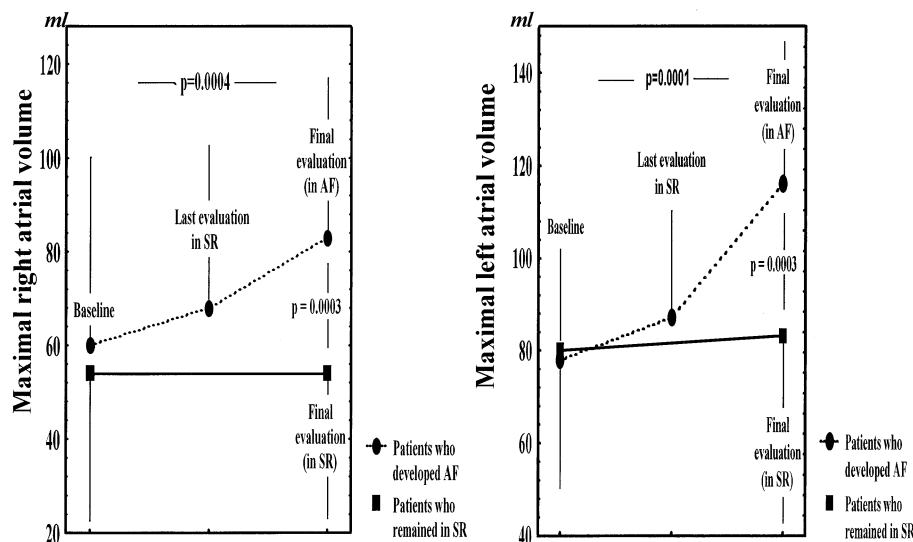


### Prognostic significance of development of chronic AF.

Despite anticoagulation, 3 of 18 patients experienced a stroke, which was fatal in 2. At the time of the events the INR was 1.5, 2.0 and 2.6, respectively. Systemic thromboembolism (two strokes and two peripheral emboli) occurred in only 4 (1.2%) of the 326 patients with SR, 128 of whom (39%) received anticoagulation. Major cardiac events (27 sudden deaths, 61 pump failure deaths, 26 urgent heart transplantations) occurred in 114 (33%) of the 344 patients. Of the 18 patients who developed chronic AF, 9 had a major event (50%). When the first 300 days from the onset were considered, AF was significantly associated ( $p = 0.02$ , OR 4) with cardiac events, whereas it had no influence on patients who survived longer than that period.

### Discussion

It is commonly believed that AF exerts a negative hemodynamic effect because of the loss of atrial transport and impairment of ventricular rate control, reduces exercise performance, predisposes to systemic thromboembolism and triggers left ventricular arrhythmias. It has seemed reasonable to postulate that these unfavorable effects may become particularly deleterious in patients with CHF and a limited cardiac reserve, an impaired exercise tolerance and higher risk of thromboembo-



**Figure 4.** Changes in right and left atrial maximal volumes over time in patients who developed AF versus those who remained in SR.

lism and ventricular arrhythmias. Paradoxically, the belief that AF adversely influences morbidity and mortality in these patients has been recently challenged (8–11).

However, all previous studies investigated patients with AF already present versus those with SR, which raises concerns regarding the likelihood of selection bias. In fact, the most compromised patients (who may not have survived long after the onset of the arrhythmia) were likely to have been excluded, whereas patients in whom AF was the cause of the occurrence of CHF (a relatively benign condition reversible after slowing heart rate) were likely to have been included. This selection may limit the practical value of the results of these studies in patients with CHF who develop primary AF.

In the present study we prospectively investigated a large group of patients with CHF and SR. Our results show that in these patients, the occurrence of AF cannot be predicted by any baseline variable, whereas previous episodes of reversible AF, reduced left atrial contribution to filling and reduced atrial emptying fraction, observed during follow-up, were significantly associated with a later occurrence of AF. Furthermore, our study demonstrates that the occurrence of AF is associated

with clinical and hemodynamic deterioration and may predispose to systemic thromboembolism.

**Predictors of chronic AF.** Several mechanisms, all of which may potentially operate in CHF, may facilitate the onset and maintenance of AF. Increased left atrial size and pressure are generally believed to be important in the genesis of AF and are regarded as causes of unsuccessful cardioversion and late recurrence of the arrhythmia (18–22). In our study many patients remained in stable SR despite markedly dilated atria and elevated pressures. Furthermore, no differences were found in atrial volumes or in right atrial and pulmonary artery wedge pressures between patients who subsequently did or did not develop AF. Perhaps the slow progression of the disease allows a certain adaptation that minimizes the electrophysiologic effects of atrial wall distension and could explain the preservation of SR in many patients with CHF. This adaptation may also account for the surprising finding that left atrial dimensions were not predictive of conversion of AF to SR. Autonomic tone and thyroid dysfunction may also play a relevant role in the genesis of AF (23,24). Serum norepinephrine and baroreflex sensitivity greatly varied among patients and were not predictive of the onset of AF. Moreover, in the present study all patients who had AF were euthyroid.

In our experience, the only variables associated with later onset of AF were the occurrence of reversible AF and the reduction of the left atrial contribution to filling. The latter is a new finding. Two factors may lead to the reduction of the left atrial contribution to filling: an increase in left atrial afterload because of a stiff left ventricle or, alternatively, a deterioration of left atrial pump function (25,26). The finding that pulmonary artery wedge pressure and the early diastolic deceleration time of mitral flow (an indicator of left ventricular stiffness) did not change points to the second mechanism and suggests that in CHF the onset of AF is preceded by left atrial mechanical dysfunction. An “atrial myopathy,” not entirely dependent on mechanical overload, has been previously described in various

**Table 4.** Significance of Differences in Variables During Follow-Up in Measurements Obtained in Patients with Atrial Fibrillation (before and after the event) and in Those Remaining in Sinus Rhythm

	F Value	p Value
NYHA functional class	5.3	NS
Peak $\text{VO}_2$ (ml/kg per min)	16.8	0.0001
Pulmonary artery wedge pressure (mm Hg)	5	NS
Cardiac index (liters/min per $\text{m}^2$ )	8.9	0.003
Maximal left atrial volume (ml)	9.1	0.003
Maximal right atrial volume (ml)	13.6	0.0003
Tricuspid regurgitation (4-grade score)	7.4	0.002
Mitral regurgitation (4-grade score)	15.9	0.0001

Abbreviations as in Table 1.

types of cardiomyopathies (27–29), and ischemia and fibrosis of atrial myocardium may well occur in patients with ischemic cardiomyopathy. However, the relation of such dysfunction to later development of AF has not yet been described.

**Clinical and hemodynamic changes associated with AF.** Despite an already impaired atrial transport, the development of AF was associated with relevant clinical and hemodynamic deterioration. The finding that the deterioration did not occur from baseline to the last evaluation in SR, whereas it was observed after the onset of AF, suggests that AF may play a pathogenetic role in its determination. However, because of the relatively long interval between the last evaluation in SR and the onset of AF, it cannot be proved whether AF is the cause or simply a marker of such deterioration. We can never know the answer to this “chicken or the egg” question because the pre-AF evaluation can inevitably only be performed at some point before the onset of AF. However, arguments can be made for a causal association by comparison of our data with those obtained in previous studies.

The association between AF and exercise performance has been extensively investigated, yielding discordant results (4,7,30–32). Some studies that compared patients with CHF with and without AF failed to demonstrate any significant difference in exercise tolerance (7). In contrast, other studies investigating patients before and after cardioversion found an improvement (4,30). Our findings are in line with those observed after cardioversion and show that the development of AF from SR is associated with a reduction in exercise tolerance despite the higher exercise heart rates that were reached. Lack of hemodynamic monitoring during exercise limits the interpretation of these results. It can be hypothesized that impaired ventricular filling or an increase in mitral and tricuspid regurgitation may have reduced cardiac index during exercise.

At rest, cardiac index was indeed much lower after the onset of AF. The importance of atrial contribution to filling in the maintenance of cardiac output was recognized several decades ago (33). However, in patients with severe CHF and elevated left ventricular filling pressures, left atrial transport is considered less important (26). Confirming this observation we found that left ventricular filling at atrial contraction was impaired in many patients, particularly in those who later developed AF. Yet, after loss of atrial transport because of AF, cardiac index decreased by ~20%. Loss of right atrial transport (not assessed in the present study), the ineffectiveness of the ventricles to generate significant outflow because of a too short ECG RR interval and worsening in mitral and tricuspid regurgitation may explain this finding.

Vigorous, synchronized atrial contraction has long been recognized as an important factor in determining the closure of mitral and tricuspid valves and in preventing regurgitation (34–36). The absence of these contractions may be particularly deleterious in patients with dilated ventricles and may offer a plausible explanation for the increased severity of mitral and tricuspid regurgitation observed after the onset of AF.

Another potentially adverse effect of AF was the marked increase in left and right atrial volumes. There has been

intense debate on the cause/effect relation between AF and atrial enlargement (18,37,38). It was recently shown (38) that in patients with normal left ventricular function, atrial enlargement follows the onset of AF. Concordantly, in our study atrial dimensions increased in the evaluation after the onset of AF, however, atrial volumes were much greater, and their increase was documented sooner after the development of the arrhythmia. The effects of AF, combined with those of elevated atrial pressures and valvular regurgitations, may have further contributed to atrial dilation in our patients with CHF. Whatever the mechanism, left atrial enlargement may predispose to systemic thromboembolism (39). Indeed 3 of the 18 patients who developed chronic AF had a stroke within a few months. This finding confirms the results of one of our previous studies, which showed that in patients with chronic CHF, AF associated with low cardiac output is a strong predictor of thromboembolic risk (40). However, other reports failed to demonstrate this association, probably because of increased use of anticoagulant agents in patients with a presumed higher risk (i.e., those with AF) (8,10). There is similar uncertainty concerning the relation of AF to mortality in patients with CHF (6,9,11,41). In our study, in which the impact of AF could be assessed from its onset (albeit in a limited cohort), major cardiac events occurred relatively soon after the onset of AF in half of the patients.

**Limitations and conclusions.** Some limitations of the study must be acknowledged: 1) The study was carried out in a referral center recruiting patients from all of Italy. For this reason, the frequency of serial evaluations established by the protocol was kept to a minimum, so that the time interval between the last evaluation in SR and the event was variable and, in some patients, rather long. 2) Although patients were carefully followed up, it cannot be ruled out that some of those who were classified as having stable SR had episodes of undocumented AF, and conversely those classified with chronic AF may have had intermittent phases of SR. 3) The number of patients who developed AF was too small to draw firm conclusions regarding the prognostic significance of AF. Despite these limitations the present study shows that in patients with CHF and SR, the development of AF is not infrequent. Its prediction, despite the large set of variables considered, remains elusive. Only previous episodes of reversible AF and an impaired left atrial contribution to filling observed during follow-up were associated with an increased risk of developing chronic AF, but the low specificity of the model obtained limits the practical value of these findings. Perhaps, we can speculate that patients with reversible AF should be medically treated (with amiodarone or beta-adrenergic blocking agents), and those with a progressive decrease in atrial transport should be unloaded by a more aggressive vasodilator in an attempt to maximize preservation of atrial function and prevent chronic AF. Primary AF is associated with relevant clinical and hemodynamic deterioration, predisposes to thromboembolism and is linked to a poor prognosis. If AF is at least in part a cause of the deterioration, more aggressive attempts to prevent and cardiovert AF might

improve prognosis. However, further studies aimed directly at this point are needed.

We thank Rachel Stenner, MBBS, for help in the preparation of the manuscript.

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